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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/757,775	01/14/2004	Rodney J. Ho	2606-3342-4557PT	5476

34395 7590 11/09/2009

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EXAMINER	
RAMACHANDRAN, UMAMAHESWARI	
ART UNIT	PAPER NUMBER
1627	
MAIL DATE	DELIVERY MODE
11/09/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/757,775	HO ET AL.	
	Examiner	Art Unit	
	UMAMAHESWARI RAMACHANDRAN	1627	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 June 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-9 and 15-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5-9 and 15-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The examiner notes the receipt of the amendments and remarks, and the affidavits received in the office 6/29/2009. Claims 3, 5-9,18-45 have been cancelled. Claim1 has been amended. Claims 10-14 are withdrawn from consideration. Claims 1-3, 5-9 and 15-17 are pending and are being examined on the merits herein.

Response to Arguments

Applicants' arguments and the affidavits received in the office on 6/29/2009 have been fully considered. Applicants' amendment necessitated the withdrawal of the 102(b) rejection anticipated by Bergeron et al. Applicants' amendment necessitated the modified rejections presented in this office action. Accordingly, the action is made non-final.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-3, 5, 7-9, 15-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kirpotin (U.S. 6,110,491, effective filing date, Oct 22 1996).

Kirpotin teaches a liposome composition containing an encapsulated compound and a method of producing the composition. Kirpotin teach exemplary vesicle-forming lipids include the phospholipids, such as phosphatidylcholine, phosphatidic acid, phosphatidylethanolamine, phosphatidylinositol and other suitable lipids include glycolipids, and sterols such as cholesterol (col. 9, 25-28). The reference further teach suitable compounds in the liposome complex preparation include low water solubility compounds preferably in the pH range of 3-9 such as HIV protease inhibitors including indinavir, ritonavair etc. (col. 7, lines 54-56, col. 8, lines 32-33). The reference also teach liposomes composed of the lipids egg phosphatidycholine (PC), cholesterol (CHOL) and teach lipid to drug ratio of 1μm to 200 nm (example 1) which is 5:1. The references teaches that bulk phase pH of the suspension can be within the range pH 6-8 suitable for parenteral use (col. 8, lines 39-40). Kirpotin teaches that liposomes can be prepared in the desired size range, typically between 0.03-1 micron, preferably between 0.03 to 0.5 microns and further teaches that homogenization methods are also useful for down-sizing liposomes to sizes of 100 nm or less (col. 10, lines 1-12).

It would have been obvious to one of ordinary skill in the art to formulate a lipid drug complex because of the teachings of Kirpotin. The reference teaches a liposome composition containing an encapsulated compound and a method of producing the

composition. One of ordinary skill in the art would have been motivated to formulate a lipid-drug complex because of expectation of success as Kirpotin teaches lipid drug complexes with the lipids including phosphatidylcholine. The references do not explicitly teach that the drug substantially dissociates from the lipid-drug complex within a pH range of 5.0-5.5. Kirpotin teach the same components of the lipid-drug complex, the drug indinavir can be entrapped in a liposome as claimed in the instant application. The dissociation of the drug from the complex at the claimed pH range is the property of the lipid-drug complex. Regarding the claimed dissociation properties, the Office does not have the facilities for examining and comparing applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same functional characteristics of the claimed product. In the absence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences. See *Ex parte Phillips*, 28 U.S.P.Q.2d 1302, 1303 (PTO Bd. Pat. App. & Int. 1993), *Ex parte Gray*, 10 USPQ2d 1922, 1923 (PTO Bd. Pat. App. & Int.) and *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977). It would have been obvious to one of ordinary skill in the art at the time of the invention to formulate a lipid-drug complex of 50-80 nm in diameter (as claimed in claim 17) because of the teachings of Kirpotin et al. Kirpotin teach that the liposomes can be prepared in the size range of 100 nm or less. Size is a result effective parameter that a person of ordinary skill in the art would routinely optimize. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ. It would have been customary for an artisan of

ordinary skill to determine the optimal size of the vesicles in order to best achieve the desired results. Thus, absent some demonstration of unexpected results from the claimed parameters, this optimization of ingredient amount would have been obvious at the time of applicant's invention.

Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kirpotin (U.S. 6,110,491) as applied to claims 1-5, 7-9, 15-17 above and in view of Thibodeau (Molecular Engineering, 1991, 275-293) and Konigsberg et al. (U.S. 5,258,499).

Kirpotin's teachings discussed as above.

Kirpotin does not teach the liposome to be unilamellar.

Thibodeau teach the role of liposomes in antigen delivery, preparation of liposomes and further teach that the most commonly used lipids are phospholipids, major structural components of biological membranes and the most common phospholipid is phosphatidyl choline (PC) (p 276, para 4). The reference also teach that the liposomes may differ with respect to dimension (from 25 nm to several microns in diameter) and structure (monolamellar or multilamellar). The reference also teaches the preparation of unilamellar liposome (p 281, preparation of immunosomes).

Konigsberg et al. teach delivery vehicle formulations comprising active agents encapsulated within liposomal vehicles (see Abstract). The reference teach that unilamellar liposomal liposomes have been shown to be useful in targeting solid tumors and to have greater circulation times than other vehicles (col. 15, lines 29-32).

It would have been obvious to one of ordinary skill in the art at the time of the invention to make a lipid drug complex where the liposome is unilamellar because of the teachings of Thibodeau and Konigsberg et al. Thibodeau teach the preparation of unilamellar liposomes in antigen delivery and Konigsberg et al. teach that unilamellar liposomal liposomes have been shown to be useful in targeting solid tumors and to have greater circulation times than other vehicles. One of ordinary skill in the art would have been motivated in expectation of success in preparation of unilamellar liposomes from Thibodeau's teachings and to target solid tumors and for greater circulation times than other vehicles by formulating unilamellar liposomes as stated by Konigsberg.

Claims 1-3, 5-9, 15-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bergeron et al. (U.S. 5,773,027) in view of Kirpotin (U.S. 6,110,491, effective filing date, Oct 22 1996).

Bergeron et al. teaches formulation of liposomes for the treatment of a viral disease which comprises: 1) a lipid component comprising a mixture of diacylphosphatidylcholine and diacylphosphatidyl glycerol and ii) a therapeutic amount of an entrapped drug such as saquinavir effective against said viral disease (see Abstract, claims 1 and 5-10). The reference teaches the preparation of unilamellar liposomes (col. 4, line 53). The reference teaches the intravenous administration of liposomes to rats (Table 3). The reference teaches the same drug (saquinavir) as claimed in claim 9 of the instant application. Hence this meets the limitation of at least one drug molecule having low aqueous solubility within a neutral pH range.

The reference does not teach indinavir (elected species) as the drug and phosphatidyl choline (elected species) as the lipid in the lipid-drug complex.

Kirpotin's teachings discussed as above. Kirpotin teach the same components of the lipid-drug complex, the drug indinavir can be entrapped in a liposome as claimed in the instant application. The reference also teaches that the lipid-drug complex can be parenterally administered and subcutaneous administration is a type of parenteral administration.

It would have been obvious to one of ordinary skill in the art to formulate a lipid drug complex comprising indinavir as the drug and phosphatidylcholine as the lipid in the lipid-drug complex because of the teachings of Kirpotin. The reference teaches a formulation comprising the lipid and a drug and further teaches phosphatidylcholine as one of the exemplary lipid. One of ordinary skill in the art at the time of invention would have been motivated to formulate indinavir as the drug in the lipid-drug complex because Kirpotin teaches the equivalence of indinavir and saquinavir. Also one of ordinary skill in the art at the time of invention would have been motivated to achieve similar or better therapeutic benefits in using one anti-HIV drug for another in the formulation. One of ordinary skill in the art would have been motivated to formulate a lipid-drug complex using phosphatidylcholine because of expectation of success as Kirpotin teaches lipid drug complexes with the lipids including phosphatidylcholine. The references do not explicitly teach that the drug substantially dissociates from the lipid-drug complex within a pH range of 5.0-5.5. Kirpotin teach the same components of the lipid-drug complex, the drug indinavir can be entrapped in a liposome as claimed in the

instant application. The dissociation of the drug from the complex at the claimed pH range is the property of the lipid-drug complex. Regarding the claimed dissociation properties, the Office does not have the facilities for examining and comparing applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same functional characteristics of the claimed product. In the absence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences. See *Ex parte Phillips*, 28 U.S.P.Q.2d 1302, 1303 (PTO Bd. Pat. App. & Int. 1993), *Ex parte Gray*, 10 USPQ2d 1922, 1923 (PTO Bd. Pat. App. & Int.) and *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

Response to Arguments

Applicants' argue that Kirpotin and Bergeron use different techniques to prepare the claimed drug complex and there is no reason to suspect or speculate that Kirpotin's compound-loaded liposomes would necessarily release the precipitated drug when the pH of the solution containing the liposomes is lowered to between pH 5.0 and pH 5.5. In response, the claimed invention is for a composition and a method of preparing the complex with the same components as claimed need not differ in their properties. As such claim 1 comprises of two components a lipid and a drug and the prior art teaches a formulation the claimed lipid and drug and it is assumed that the formulation will have the same properties of the composition as claimed. As stated above, Regarding the claimed dissociation properties, the Office does not have the facilities for examining and comparing applicant's product with the product of the prior art in order to establish that

the product of the prior art does not possess the same functional characteristics of the claimed product. In the absence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences. See *Ex parte Phillips*, 28 U.S.P.Q.2d 1302, 1303 (PTO Bd. Pat. App. & Int. 1993), *Ex parte Gray*, 10 USPQ2d 1922, 1923 (PTO Bd. Pat. App. & Int.) and *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977). Also, Applicants' argue that Kirpotin's compound-loaded liposomes have been made by different technique other than the instant application and would not necessarily release the precipitated drug when the pH of the solution containing the liposomes is lowered to between pH 5.0 and pH 5.5. However Applicant and further state that have not provided any data or evidence to prove that the prior art formulation do not possess such properties.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the modified rejections presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Umamaheswari Ramachandran whose telephone number is 571-272-9926. The examiner can normally be reached on M-F 8:30 AM - 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1627